Toxins

Introduction

Toxins are compounds that cause human disease. Exotoxins and endotoxin are not related in any way, except that they both have the word "toxin" in them and are synthesized from bacterial DNA.

Exotoxins are made by a bacterium, are secreted into the environment, are protein with enzymatic activity, and target specific channels on specific human cells. Exotoxins are highly variable. Only specific species of bacteria make any exotoxin, and any one species makes that species' exotoxin. That unique exotoxin is going to cause a specific, unique disease in humans. There are many exotoxins. There are many bacteria. Any bacterium, Gram negative, Gram positive, acid-fast, whatever, CAN make an exotoxin. Most don't.

Endotoxin is a component of the outer plasma membrane. Not endotoxinS, but endotoxin. One of them. Endotoxin is a compound synthesized by a bacterium that can lead to human disease, so it is indeed a toxin. But there aren't multiple endotoxins. There isn't this endotoxin made by this bacterium, and that endotoxin made by that bacterium, or this bacteria's endotoxin has this mechanism where that bacteria's endotoxin has that mechanism. Endotoxin is lipopolysaccharide (LPS), a constituent of the Gram-negative cells' outer plasma membrane. Like phospholipid or cholesterol are to us, lipopolysaccharide is to the bacterium—part of the plasma membrane. Humans don't have endotoxin. Bacteria do. When human immune cells see endotoxin, they recognize it as foreign. Endotoxin doesn't DO anything except get noticed by the immune system.

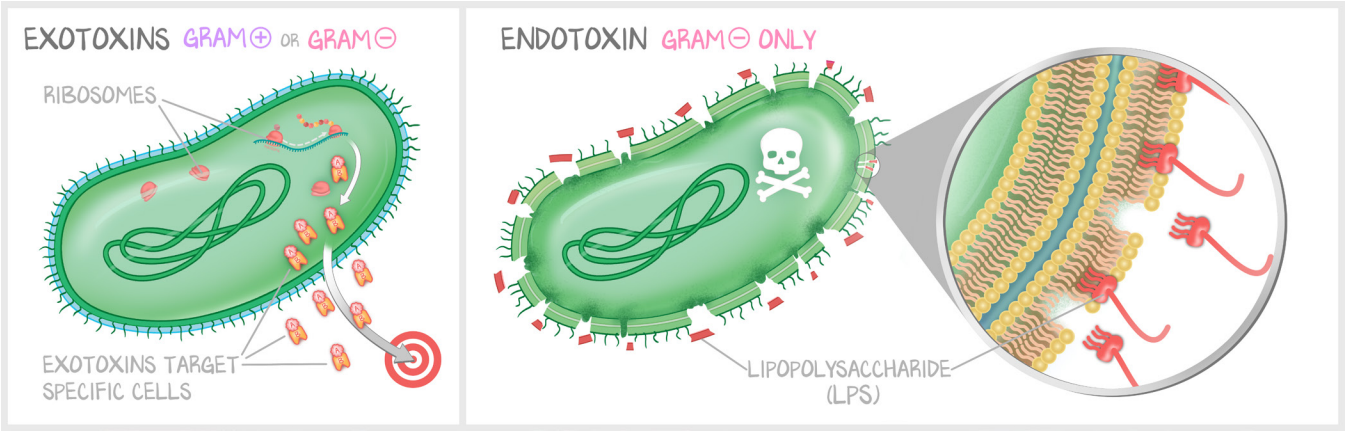

Figure 3.1: Endotoxin and Exotoxins—What's the Deal?
Exotoxins are proteins synthesized from amino acids by ribosomes, then released into the extracellular space to help the bacterium stay alive. They exhibit tropism, have a specific effect, and can be produced by Gram-negative and Gram-positive organisms. Meanwhile, endotoxin is part of the outer plasma membrane of Gram-negative organisms and is only exposed to the human immune system when a bacterium dies. It is not meant to be secreted or have an effect, nor does it exhibit tropism. Endotoxin kills by inducing inflammation (see later). Exotoxin causes symptoms by affecting a specific cell type and targets a particular cellular mechanism of that specific cell type.

We're going to cover endotoxin first, then the generalities of exotoxins, and then go exotoxin by exotoxin. Because you are not supposed to have seen the lessons on the specific bugs yet, we focus on the mechanism of action of toxin, mention briefly the presentation, but reserve that discussion for the lessons about the specific bugs. This lesson is about categorization by mechanism of toxin.

Endotoxin

Endotoxin is a thing Gram-negative bacteria make as part of their plasma membrane. Endotoxin happens to cause human disease when the bacterium dies. Endotoxin is part of the bacterium, is not secreted, has no enzymatic activity, induces nonspecific human responses, and requires high concentrations to have any effect on humans. Said differently, endotoxin is **not secreted**, **not enzymatically active**, and is **poorly antigenic.**

BUT. Endotoxin is the thing that kills people when they are infected because they have a generalized inflammatory response that impacts the entire human. It is not the effect of the endotoxin that causes the human to get sick. The endotoxin doesn't do anything to human cells. Think of endotoxin as an antigen, as foreign material that macrophages identify as foreign. That identification initiates an inflammatory response. If all that happened were inflammation at the site of infection, the innate immune system would be doing its job—increasing arterial flow in, decreasing venous flow out, vasodilating blood vessels to let macrophages out of the blood and into the tissue. But if there is **widespread, systemic activation** of the same function, you get vasodilation everywhere. Vasodilation everywhere means a compromise of systemic vascular resistance. This is septic shock.

This is how endotoxin kills. When there is enough endotoxin to elicit inflammation, endotoxin, or at least the inflammatory response to endotoxin, is what kills humans.

Endotoxin is found in the outer plasma membrane. Because endotoxin is in the outer plasma membrane, only **Gram-negative rods** can have endotoxin. Endotoxin (endo, within) is **not secreted**—its "release" is a byproduct of cell lysis or detached blebs of a necrosing cell. The death of a Gram-negative cell results in its plasma membrane's fracturing, exposing what had been contained in the lipid bilayer. The endotoxin we're referring to is **lipopolysaccharide** (LPS). Lipo (fat) poly (many) saccharide (sugar) is lipid and sugar. The toxic portion is **lipid A**, usually hidden within the membrane. There are no amino acids. Peptides are immunogenic. Therefore, endotoxin is poorly immunogenic (it does not induce the formation of antibodies). Endotoxin has no enzymatic effect, no target protein, so it cannot be made into a toxoid. Poorly immunogenic and no toxic component makes for a poor target for a vaccine. There are no vaccines available against endotoxin. It wouldn't do much anyway if there were, since antibodies against LPS would not be able to identify it until the Gram-negative organism was already dead and lysed.

Endotoxin is not designed to kill the host, defend from other cells, or escape immunity. Endotoxin is part of the outer membrane, intrinsic to how bacterial cell membranes are. Not function, but are. Therefore, it makes sense that there is no secretion of these molecules and that the genes that code for endotoxin are in the **chromosomal DNA**. Because endotoxin is made of lipid, and lipids do not denature, endotoxin is **heat stable**, able to last for **over an hour at 100°C** (212°F).

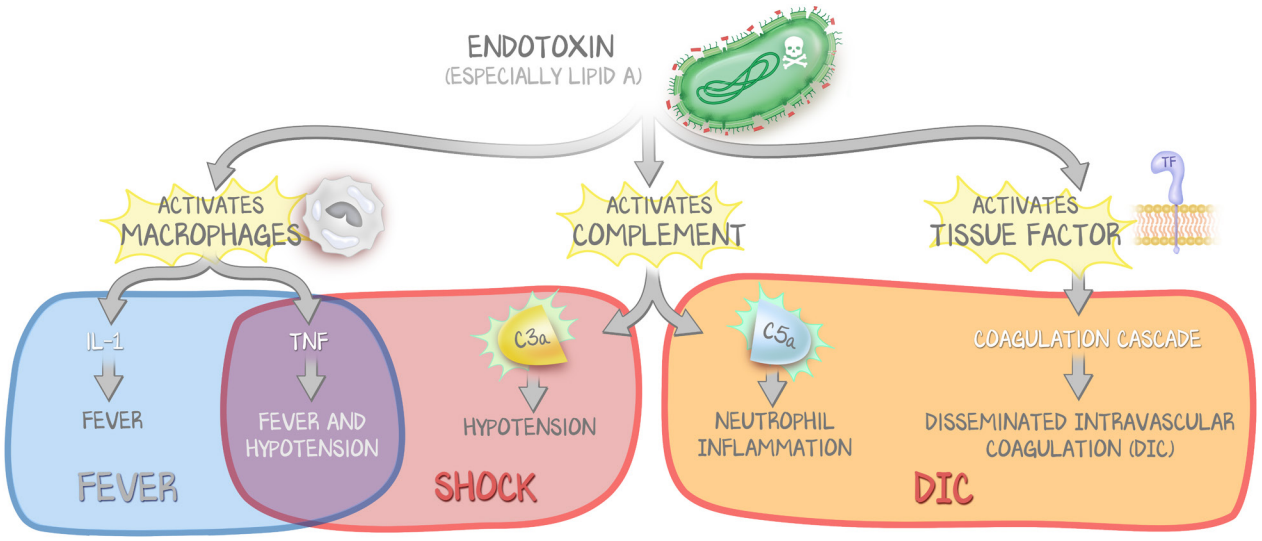

Figure 3.2: Endotoxin and Its Effects
Endotoxin is released from the outer membrane of Gram-negative bacteria as the bacteria die. The things people die from—shock and DIC—are all because of our own host response to endotoxin. Use this illustration to follow along with the text that follows.

How endotoxin causes human disease—macrophages, complement, coagulation.

1. **Activation of macrophages** by binding of LPS to macrophage receptor leads to the release of pro-inflammatory cytokines which produce **fever** (**IL-1, IL-6** and **TNF-α**) and vasodilatory compounds that cause **hypotension** (**nitric oxide**). This is the same response as when the phagocyte encounters something foreign and is not directed by the adaptive immune system (those PAMPs and PPRPs from Immunology #4: *Innate Immune System*). There it caused vasodilation and altered endothelial cell expression in order to get the leukocytes to the site of infection. When vasodilation happens everywhere at once, you get systemic hypotension.

2. **Activation of complement.** Endotoxin promotes the formation of C3a and C5a, which in turn causes release of **histamine** (vasodilation, worsening hypotension) and affects neutrophil chemotaxis. "Demargination" causes the white blood cell count to rise in acute inflammation separate from the production of more immune cells by the bone marrow, a product of C5a within the lumen of the blood. A leukocytosis without bandemia is a marker of inflammation. Bands (immature white blood cells released from marrow early) causing the leukocytosis is a sign of infection.

3. **Activation of the coagulation cascade.** LPS causes fever and leukocytosis. LPS can cause hypotension. LPS rarely activates the coagulation cascade—the mechanism by which LPS provokes disseminated intravascular coagulation. Clots form where they shouldn't, using up all the resources for clotting, so clots can't form where they should. The patient drops their platelets and hemoglobin, bleeds from everywhere, and clots in the deep veins.

We've harped on the fact that there is ONE endotoxin. However, just as the O-antigen can vary a little between organisms, so too can the toxic lipid vary a little. This is why some Gram-negative bacteria are more dangerous than others. *E. coli*'s LPS is one of the most antigenic, being found in a large number of septic shock patients. But think of how few times you've heard of septic shock from syphilis (*Treponema pallidum*). They are both Gram-negatives, both have LPS, but it just happens to be the case that *E. coli*'s is more antigenic and therefore provokes a more systemic inflammation. As an aside, teichoic acid is the Gram-positive equivalent of LPS. We want you learning there is AN endotoxin, LPS, found in the membrane of Gram-negative organisms. But technically, there are endotoxins. We felt that separating it

(endotoxin) from them (exotoxins) helped solidify the concept. Because endotoxin is part of the plasma membrane and not secreted, it should not be compared to exotoxins, which are protein molecules actively secreted to carry out an enzymatic effect. The rest of the lesson is about exotoxins. Each cell has its own exotoxin, if it produces an exotoxin at all.

EXOTOXINS		ENDOTOXINS
Yes	Secreted	No
Yes	Enzymatic Activity	No
Extracellular	Relationship to Cell	Part of cell membrane
Protein	Main Component	Lipid
High (< 1 ug)	Toxicity	Low (> 100 ug)
When secreted, induces high titers, immunogenic, and possible vaccine	Antigenic	When cell dies, poorly antigenic, not immunogenic, no vaccine
Plasmid	DNA	Chromosomal
Toxoids	Vaccines	No
Destroyed at high heat (60°C)	Stability	Stable at high heat (100°F)
Toxins activate specific channels on specific cells	How Influences Disease	Systemic macrophages induce systemic activation
Various effects based on which toxin it is	What They Cause	Fever, hypotension, leukocytosis, DIC
The toxin itself	What Causes the Disease	Immune response to toxin presence

Table 3.1: Endotoxin vs. Exotoxin—The Wrong Thing to Do
Do not memorize this table. Exotoxins are one thing, secreted by bacteria, demonstrating strict tropism for a cell type and having an intended effect. Endotoxins are a completely separate entity that exists only in the outer plasma membrane of Gram-negative organisms. The only thing they share, the only reason to compare them, is that they start with the letter E and end in -toxin. This table, or a variation of it, exists in every text on the subject. We still are uncertain why. We relented to outside influence (people we trust on the topic) and made our own.

Exotoxins in General

Exotoxins are **actively secreted** from bacteria, have enzymatic activity, and target a specific type of human cell (high specificity). Even at very small doses, exotoxins have a significant effect (high toxicity).

Exotoxins are formed by **Gram-negative** AND **Gram-positive** bacteria. The toxins themselves are **polypeptides** (they are proteins made from amino acids). The genes that code for exotoxins are usually found on **plasmids** or in **lysogenic bacterial viruses**. Because these exotoxins are peptides and are extracellular, they are **highly antigenic** and can induce the synthesis of protective antibodies called antitoxins. An exotoxin has an antigenic component which is always different than the toxic component (we saw this in Immunology #13: *Vaccines*). If the toxic portion is removed (the vaccine lacks the toxic portion, so does not cause disease), the exotoxin can be turned into a **toxoid** in which the antigenic portion remains intact (vaccine promotes the formation of antibodies).

Many exotoxins (but not all) are **AB toxins**. In this arrangement there is an **A (active) subunit** that possesses enzymatic activity; it does something to a target. We will see several variants of "enzymatic activity" in the remainder of this lesson—it will be the mechanism of action against human cells. Suffice it to say that the A subunit does the thing the toxin does, and is the portion removed to make a toxoid. The **B (binding) subunit** is responsible for binding the exotoxin to specific receptors on the human cell plasma membrane. Any one exotoxin has a binding subunit that identifies a specific protein on the plasma membrane of a specific cell. The binding of B determines **where the toxin will take effect**; A causes the **toxic effect**.

Because toxins are proteins, and heat denatures proteins, exotoxins are generally **heat labile**—they are destroyed at temperatures that exceed 60°C (140°F). Some exotoxins that are AB toxins are heat stable, and some AB toxins are heat labile, and some are not AB toxins. Learn that all exotoxins are AB proteins and are heat labile as a blanket statement, and we'll point out the exceptions along the way.

The way the rest of this lesson plays out surrounds the mechanism of action of each toxin. What we've tried to do is show you the overlap to make these toxins easier to study. You should NOT see each row in the final table as a discrete object to recall. Start putting bugs and their exotoxins into buckets—for example, preformed enterotoxins cause emesis, enterotoxins formed after bacterial infection is established cause diarrhea, and Shiga-like toxins cause dysentery. Do not be misled by ADP-ribosylation; you will see it as an A-subunit mechanism across multiple exotoxin types. Pay attention to its target.

Exotoxins That Inhibit Protein Synthesis

These exotoxins are going to affect human eukaryotic translation. Human eukaryotic translation requires the 60s and 40s ribosomes to converge, become the 80s ribosome, then start reading codon after codon, translating the mRNA into an amino acid sequence. This process requires elongation factor-2 (EF-2) to progress. There are two mechanisms of action of exotoxins that affect protein translation: **ADP-ribosylation of EF-2** and **removal of adenine from the 60s ribosomal subunit**. Use caution: exotoxin ADP-ribosylation inhibits EF-2, inhibiting protein translation. This is not E2F, the transcription factor for the cell cycle G_1 checkpoint.

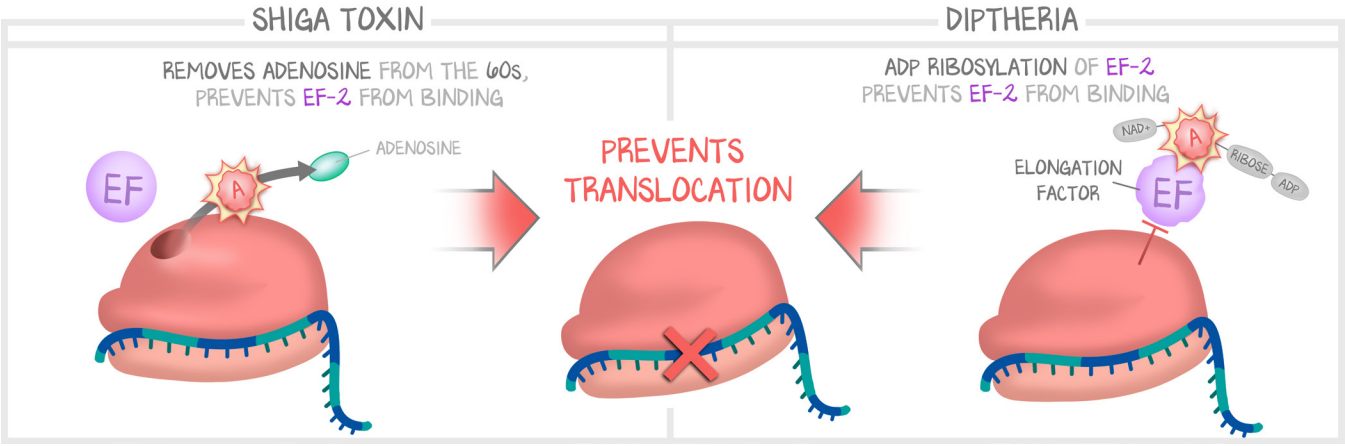

Figure 3.3: Exotoxins That Inhibit Protein Synthesis
Elongation factor 2 (EF-2) normally binds to the 60s ribosome, stabilizing the incoming tRNA. Shiga toxin removes an adenosine from the 60s, preventing EF-2 from binding. Diphtheria toxin ADP-ribosylates EF-2, preventing EF-2 from binding the 60s ribosome. Both result in the same thing—EF-2 failing to bind to 60s and therefore halting translocation—but do it in very different ways.

Shigella dysenteriae and *enterohemorrhagic E. coli* (EHEC) are essentially the same bug—at least their exotoxins are. Their common A subunit causes **removal of adenine rRNA of the 60s ribosomal subunit**. The B subunit targets **enterocytes**. Infection with either of these bugs results in dysentery, **bloody diarrhea**. The A subunit has a smaller predilection for the kidney (but still greater than for other tissues). In a patient with **bloody diarrhea**, **renal failure**, and **thrombocytopenia**, consider TTP/HUS. TTP/HUS is caused by the exotoxin. In *Shigella*, the toxin is called Shiga toxin. In EHEC, the toxin is called Shiga-like toxin. Learn them as the exact same thing, except that **O157:H7** (EHEC) is found in **undercooked meat**, while *Shigella* is found in contaminated water (worldwide) or poor hand hygiene (vegetable, produce handlers in the US; daycares with dirty babies).

Corynebacterium diphtheriae causes **diphtheria**. The diphtheria toxin is an AB toxin. The A subunit inhibits eukaryotic protein synthesis through ADP-ribosylation of EF-2. The B subunit has a predilection for nonkeratinized epithelium, such as is found in the oropharynx, resulting in the **grey pseudomembrane** in the back of the throat. Attempting to remove the pseudomembrane causes hemorrhage, compromising the airway. Leaving the pseudomembrane could obstruct the airway, compromising the airway. Better to **vaccinate** against diphtheria.

Pseudomonas aeruginosa produces exotoxin A, which has the same A subunit as diphtheria. *Pseudomonas*'s B subunit targets hepatocytes. This is low yield relative to diphtheria, and remains more of a testable association, linked by the ADP-ribosylation of the EF-2 mechanism.

Exotoxins That Induce Secretion

This category of exotoxins is caused by **ADP-ribosylation of a GTP-associated protein** that leads to a rise in the activity of adenylyl cyclase, levels of cAMP, PKA activity, and subsequent downstream phosphorylation and activation of chloride channels in the apical membrane of enterocytes. There is always a balance of enterocytes that secrete salt and water (at the base of the crypts of Lieberkühn) and enterocytes that absorb salt, sugar, and water (at the tips of the villi). When the exotoxin is present, the secretion enterocytes win. Chloride is actively pumped into the lumen; then sodium, and finally water, following the osmotic pull of salt, follow. The net effect is secretion of salt and water into the lumen, no malabsorption, but a watery, secretory diarrhea.

Because these exotoxins are toxic to the enterocytes, resulting in a diarrhea, they are termed **enterotoxins**. Enterotoxins are AB toxins. The B subunit has a predilection for enterocytes. The A subunit ADP-ribosylates the GTP-associated proteins. This section discusses several enterotoxins, then shows an example of a mechanism that is very similar but is not an enterotoxin.

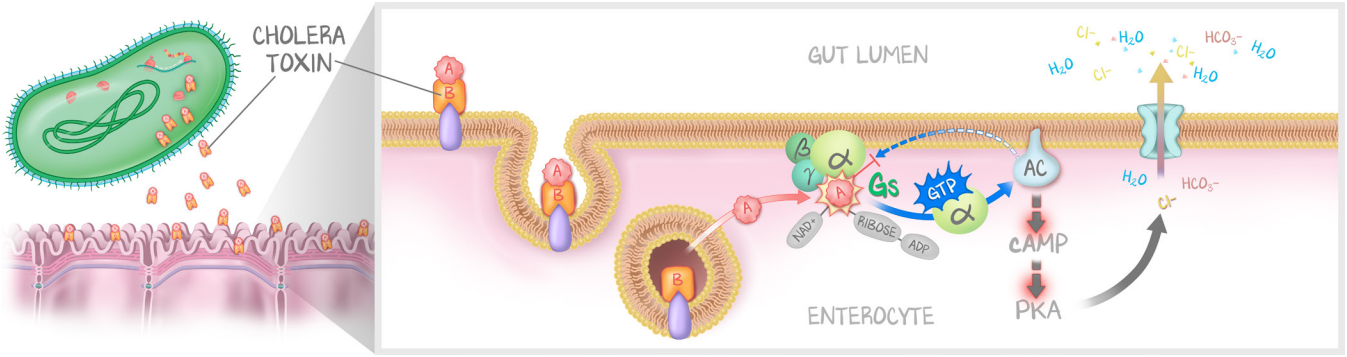

Figure 3.4: Enterotoxins
Whether it is through the ribosylation and activity of G_s or the ribosylation and inactivity of G_i, the end result is phosphorylation of downstream targets and the secretion of water, sodium, and chloride. When secretion exceeds absorption, a water secretory diarrhea occurs.

Enterotoxic *E. coli* (ETEC) causes a water diarrhea in this way. ETEC's **heat-labile** toxin is the AB toxin that causes secretory diarrhea through ADP-ribosylation of G_S. ETEC also has a separate **heat-stable toxin**. The result is the same as the heat-labile toxin—secretory diarrhea—only the heat-stable form targets the **guanylyl cyclase–cGMP** pathway (instead of AC-cAMP), but also results in activation of the chloride transporter. ETEC is associated with **traveler's diarrhea,** a self-limiting watery diarrhea when traveling in Central or South America.

Bacillus cereus is a spore former, found on **reheated rice** (Asian food buffet lines). *B. cereus* causes a secretory diarrhea through the ADP-ribosylation of G_S by an AB exotoxin. The spore in the rice is ingested by the human. The spore **germinates** back into bacteria. As the germinated bacteria, now out of its spore form, the AB exotoxin is made. The spores survive the acid of the stomach; the bacteria germinate in the intestine. Because it takes time for a spore to germinate, it causes a diarrhea 5–15 hours after ingestion. Because the AB toxin acts on enterocytes in the gut lumen, the predominating symptom is watery diarrhea. But *B. cereus* also has a heat-stable toxin. The **heat-stable toxin** is a **preformed toxin**, so takes effect immediately on ingestion. Because there is no need to germinate, this toxin causes primarily an **emesis syndrome** and starts 1–6 hours after ingestion—effect felt closer to the "in" hole.

Vibrio cholerae causes **rice-water diarrhea** when contaminated (affected) patients contaminate the water supply (by putting diarrhea stool in drinking water). Cholera is hard to get—an intact stomach epithelium and gastric acid secretion usually kills cholera. But in vulnerable populations (usually Third World or impoverished peoples without a clean water supply), *Vibrio cholerae* can cause a watery diarrhea so severe that people die. It secretes enterotoxin, so AB toxin, B targets the enterocytes, A ADP-ribosylation of G_S, and so on. But because the absorptive mechanism of the enterocytes is not compromised, and the toxin has only accelerated secretion but not blocked absorption, repletion with salt, sugar, and water into the gut lumen can save lives. Cholera is said to be rice-water diarrhea. The next time you boil rice, pour the excess water into a separate pot. That's what rice-water diarrhea looks like.

The final example is a cAMP inducer but is not an enterotoxin.

Bordetella pertussis causes **whooping cough**. The patient begins with the prodrome phase, where there are nonspecific symptoms of fever, malaise, etc. In the **catarrhal phase** there are paroxysmal fits of coughing so severe that they may pass out or vomit. Often, the prolonged coughing fits exhaust any air in the lungs, and fits are interrupted by loud long gasps for air (the whoops). Its A subunit causes **ADP-ribosylation of G_i,** inhibiting G_i, disinhibiting adenylyl cyclase, increasing cAMP, and so on. The effect is the same—cAMP levels and PKA activity rise—but through inhibiting G_i rather than activating G_S (see General Pharmacology #7: *Receptors and 2nd Messengers*). The B subunit of the AB toxin targets the epithelium of the pharynx. While the outcome is secretion and edema of the larynx and pharynx, it does not cause diarrhea. Learn pertussis as the special cAMP exotoxin—inhibits G_i and affects the throat. Pertussis is **vaccinated against** with DTaP (the acellular pertussis part of this vaccine prevents this disease).

TOXIN	MECHANISM	SYSTEM	PREFORMED	SYMPTOMS
ETEC heat labile	ADP-ribosylation G_S	↑cAMP	Produced	Diarrhea
ETEC heat stable	ADP-ribosylation G_S	↑c**G**MP	Produced	Diarrhea
B. cereus heat labile	ADP-ribosylation G_S	↑cAMP	Produced	Diarrhea
B. cereus heat stable	ADP-ribosylation G_S	↑cAMP	Preformed	Emesis
Vibrio cholerae	ADP-ribosylation G_S	↑cAMP	Produced	Diarrhea
Pertussis toxin	ADP-ribosylation G_i (inhibition)	↑cAMP	Produced	Whooping cough

Table 3.2: Enterotoxins

Neurotoxins

Clostridium species are difficult because there are four of them and each one has a toxin and each one causes a very different disease. The neurotoxin-producing *Clostridium* species will be referred to by their disease, not the species name. *Clostridium tetani* causes tetanus. *Clostridium botulinum* causes botulism.

Tetanus is caused by the release of a neurotoxin following contamination of a dirty wound. Dirty wounds involve soil, rust, or feculent material. The exotoxin is released into the wound, then migrates up the neuron via retrograde transport. Tetanus is an AB toxin and can be **vaccinated against**. In those not vaccinated, the toxin, tetanospasmin, degrades SNARE proteins, the proteins that are required for vesicular binding and therefore exocytosis of neurotransmitter from the presynaptic neuron. The nerves that are affected are **inhibitory neurons** that release **GABA or glycine**. With inhibition of inhibitory nerves, there is no stop signal, so every muscle contracts, resulting in **spastic paralysis** (discussed in Immunology #13: *Vaccines*).

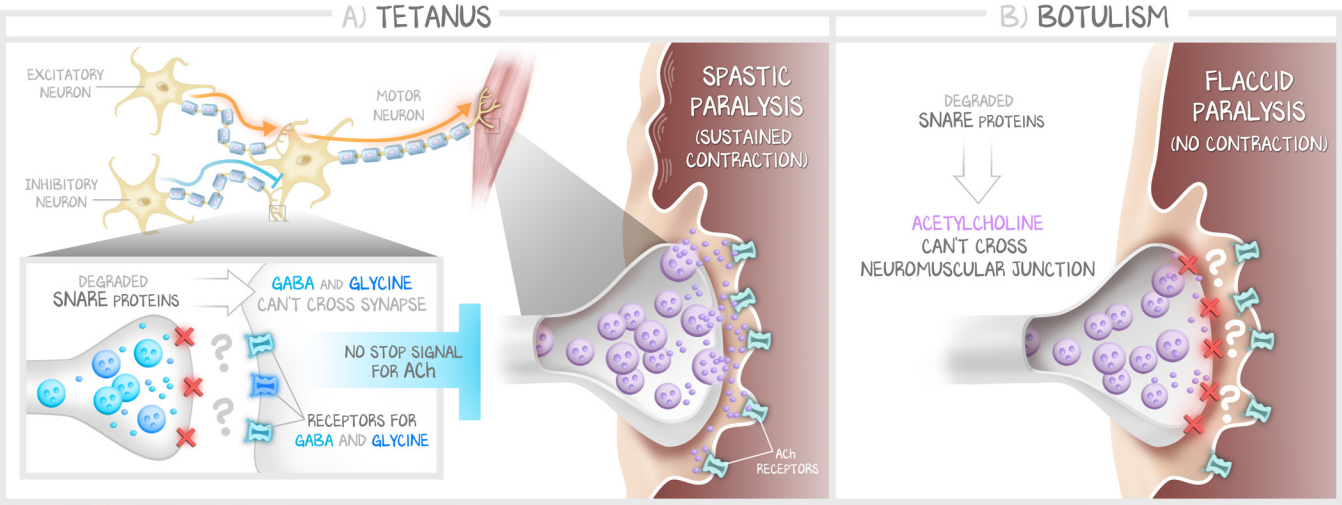

Figure 3.5: Neurotoxins
Both neurotoxins enter a specific neuron and degrade SNARE proteins, preventing the fusion of vesicles carrying neurotransmitters. (a) Tetanus affects exocytosis of vesicles from inhibitory neurons, resulting in disinhibition of the motor pathway and in spastic contractions. (b) Botulism affects exocytosis of excitatory neurons at the NMJ, resulting in the absence of contraction.

Botulism is caused by the release of a neurotoxin, usually in **contaminated honey** (babies) or **self-canned foods** (adults). It is an AB toxin that degrades SNARE proteins, but targets the excitatory motor neurons, inhibiting the exocytosis of **excitatory acetylcholine** (ACh). This results in a flaccid paralysis (death by airway compromise) when infected, or the absence of wrinkles when purposefully injected into the skin of the face (botulinum toxin is Botox).

The rest of the exotoxins in this lesson are not AB toxins.

Cell Lysis

Clostridium perfringens causes **gas gangrene**. Gas gangrene, the syndrome, is caused by several destructive enzymes released by *Clostridium perfringens*. The most important to know is **lecithinase**, a phospholipase that destroys cell membranes. In humans, lecithinase causes myonecrosis , the death of skeletal muscle and destruction of the skin above (the gangrene). In the lab, these enzymes lead to the double-bubble sign, two zones of hemolysis while growing on normal agar.

Staph. aureus causes **scalded skin syndrome**. The disease is caused by **exfoliatoxin** (also called epidermolytic toxin) that cleaves desmoglein at desmosomes. This causes the entire epithelium to separate from itself, all keratinocytes losing the connection between each other. This results in thin-walled blisters that rupture easily.

Superantigens

Superantigens function by activating T cells without MHC presentation. The compound itself is immunogenic without an antigen-presenting cell.

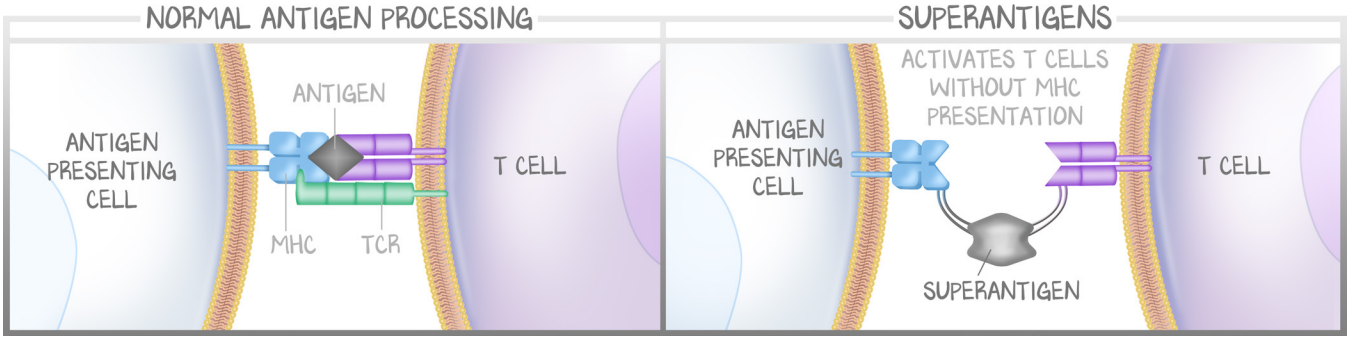

Figure 3.6: Superantigens
Normally, antigen-presenting cells phagocytose pathogens, process antigens, and then display the antigen via MHC-2 molecules in a coordinated fashion that requires receptors and coreceptors to ensure proper activation. Superantigens cross-link and activate T cells without processing antigen first. This results in uncontrolled T-cell activity and an inflammatory response far out of proportion to the threat.

Staph. aureus can also cause **toxic shock syndrome**. The exotoxin **TSST-1** (toxic shock syndrome toxin one)is not an AB toxin. It is a superantigen. Toxic shock presents with tampons left in too long OR nasal packing left in too long AND fever, rash, shock. Remove the object, treat the infection. *Strep. pyogenes* can make a superantigen like *Staph. aureus*. It is called erythrogenic exotoxin A (not to be confused with *Pseudomonas* exotoxin A) and has a mechanism of action similar to *Staph. aureus* TSST-1. It looks like toxic shock syndrome. So, if you see a toxic shock syndrome and it is NOT *Staph. aureus,* it's *Strep. pyogenes.*

Rounding Off the Toxin-Producing Bugs

Staph. aureus has a **heat-stable enterotoxin** that works just like *B. cereus*, only *Staph. aureus* is found on picnic foods with mayonnaise, ranch dressings, and potato salad. This is also a **preformed toxin**, so leads to an emesis-predominant, early-after-exposure syndrome.

Bacillus anthracis, anthrax, has lost its utility, both because anthrax is not a weapon of terror anymore and because the incidence of disease is essentially zero. But **anthrax** can be pulmonary (mediastinitis, looks like a severe pneumonia) or epidermal (cutaneous ulcers). It remains a topic of discussion because it has three exotoxins. **Edema factor** (EF) causes fluid to leak out of cells and is AC-cAMP-mediated, like

ETEC and cholera. Its **lethal factor** (LF) is a cell lysis mechanism, a protease that cleaves MAP kinase required for cell division. **Protective antigen** (PA) forms pores in human cell membranes, allowing edema factor and lethal factor to get in. AB exotoxins induce the plasma membrane into receptor-mediated endocytosis; anthrax plows right through the membrane instead.

Clostridium difficile causes *C. diff* colitis, a diarrheal illness. *C. diff* has two exotoxins. **Exotoxin A** is an enterotoxin. When exotoxin A predominates, the patient presents with a watery diarrhea, a secretory diarrhea mediated through the AC-cAMP pathway. **Exotoxin B** is a cytotoxin (cell lysis) that leads to **pseudomembrane colitis**. If the *C. diff* infection is invasive, exotoxin B predominates, and there is a bloody diarrhea.

MECHANISM	EXOTOXIN
ADP-ribosylation of G_i/G_s-AC-cAMP-PKA (or GMP) activation	*E. coli* toxins (G_s GMP, AMP) *B. cereus* toxins (G_s AMP) Cholera toxin (G_s AMP) Pertussis toxin (G_i AMP)
ADP-ribosylation of EF-2	Diphtheria toxin *Pseudomonas* exotoxin A
Removes adenine from rRNA	Shiga toxin (*Shigella*) Shiga-like toxin (EHEC)
Exocytosis inhibition of neurons	Tetanus (GABA and gly SNARE) Botulism (ACh SNARE at NMJ)
Cell lysis	*Clostridium perfringens* **α**-toxin, lecithinase *Staph. aureus* exfoliatin (scalded skin) Anthrax lethal factor
Superantigen	Toxic Shock Syndrome Toxin (*S. aureus*) Staphylococcal enterotoxin (*S. aureus*) Erythrogenic enterotoxin A (*S. pyogenes*)

Table 3.3: Alternative Organization

MECHANISM	ORGANISM	TOXIN	MODE OF ACTION (B)	TARGET (A)	ROLE IN DISEASE
Protein synthesis inhibition	*Shigella*	Shiga toxin	Removes adenine from 60s ribosomal subunit	Enterocytes (dysentery)	Stool in water, fecal-oral, day cares
	EHEC	Shiga-like toxin			O157:H7, undercooked meat
	Corynebacterium diphtheriae	Diphtheria toxin	ADP-ribosylation of EF-2	Epithelium	Pseudomembrane in throat, **vaccine**
	Pseudomonas aeruginosa	Exotoxin A		Hepatocytes	Hosts die
cAMP inducers	ETEC	Heat labile	Activation of G_S via ADP-ribosylation	Enterocytes (watery diarrhea)	Heat-stable does same, through cGMP
	B. cereus	Heat labile			Heat-stable = Emesis syndrome, preformed toxin, reheated rice Heat-stable *Staph. aureus* same, only mayo and ranch foods, picnic
	V. cholerae	Cholera toxin			Rice-water stools, watery diarrhea, fecal-oral
	Bordetella pertussis	Pertussis toxin	Inhibition of G_i via ADP-ribosylation	Pharynx	Whooping cough, **vaccine**
Neurotoxin	*Clostridium tetani*	Tetanus toxin	Protease cleaves SNARE	Inhibitory GABA, Gly of LMN	Spastic paralysis, dirty wounds, lockjaw, pain. **Vaccine**
	Clostridium botulinum	Botulinum toxin		NMJ, ACh	Flaccid paralysis, home-canned food, contaminated honey
Cell lysis	*Clostridium perfringens*	α-toxin	Lecithinase degrades cell membranes	Muscles, wounds	Myonecrosis = Gas gangrene Hemolysis = Double-bubble agar
	Staph. aureus	Exfoliatoxin	Cleaves desmoglein at desmosomes	Skin	Staphylococcus scalded skin syndrome
Superantigen (not AB)	*Staph. aureus*	TSST-1	Activates T cells without MHC presentation	Systemic	Toxic shock syndrome = fever, rash, shock, and tampons or nasal packing
	Strep. pyogenes	Erythrogenic exotoxin A			Same

Table 3.4: Summative Table Exposing Overlaps